Chapter 9

Carrier Testing for Cystic Fibrosis: Transition from Research to Clinical Practice

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About Cystic Fibrosis

Autosomal Recessive
Inheritance of two copies of a mutant gene, one from each parent, on one of the 22 autosomes (chromosomes other than X or Y).

Cystic fibrosis (CF) is one of the most common **autosomal recessive** genetic diseases in North America, occurring most frequently in Caucasian Americans of European descent, and less frequently in other racial and ethnic groups, such as African Americans and Asian Americans. CF is characterized by chronic lung disease, problems with digestion, and male infertility. Pancreatic problems occur in 85% of affected individuals, but lung function is the critical factor in prognosis and survival.

CFTR: The CF Gene

The *CFTR* gene was identified on Chromosome 7 in 1989, and controls the production of *cystic fibrosis transmembrane conductance regulator* (*CFTR*) protein. This protein controls the flow of salt and water in and out of cells, particularly those that line the lungs and digestive system. Abnormal *CFTR* protein results in reduced flow of water and build-up of thick secretions, and leads to the characteristic symptoms of CF.

Over 1,000 disease-associated changes, or mutations, have been identified in the *CFTR* gene, but most are rare. One mutation, Δ*F508*, is by far the most commonly found among Caucasians of European descent. In this group, about 1 in 25 persons is a carrier—that is, has one *CFTR* gene with a mutation and one normal *CFTR* gene. Carriers are asymptomatic and not at risk for CF. Individuals with CF have mutations in both *CFTR* genes—one from each parent—and are deficient in functional *CFTR* protein.

Cystic Fibrosis Carrier Testing

Following the release of a practice guideline on prenatal/preconception cystic fibrosis carrier testing in October of 2001, the number of pregnant women choosing to have this testing is increasing rapidly. One laboratory reported an increase from 1,000 tests per month in 2001 to 14,000 tests per month in mid-2003.[1] It is possible that as many as a million women (about 25% of all U.S. births) could be opting for testing within the next year. Understanding the history, successes and problems of this first population-based testing effort can provide

vital information about what is needed for a successful transition of a genetic test from research to clinical and public health practice in the United States.

History of CF Testing in the United States: Transition from Research to Clinical Practice

When the *CFTR* gene was discovered in 1989, widespread testing for CF mutations became a possibility. Experts cautioned, however, that screening in the general population should await improvement in the sensitivity of the test as well as the results of pilot testing.[2] In 1997, an NIH Consensus Conference reviewed existing knowledge about CF and the results of CF carrier testing pilot studies.[3] The Consensus Panel recommended that CF carrier testing should be offered to:

- couples seeking prenatal care or planning a pregnancy,
- adults with a family history of CF, and
- partners of persons with CF.

The Consensus Panel also emphasized that this testing should be phased in, to allow time for development of laboratory resources and educational materials for patients and their health care providers.

Subsequent workshops considered issues related to implementation of CF testing in routine practice.[4,5] A joint committee of the American College of Medical Genetics (ACMG), the American College of Obstetricians and Gynecologists (ACOG), and the National Human Genome Research Institute (NHGRI) was designated to coordinate the development of guidelines for provider and patient education, informed consent, and laboratory testing and reporting.

In spite of concerns about appropriate use and performance of CF testing, some consensus emerged in the following years. By 2001, some geneticists and obstetricians had begun offering this testing option to selected groups.[6,7] Widespread introduction of screening really began, however, when the ACMG published *Laboratory Standards and Guidelines for Population-Based Cystic Fibrosis Carrier Screening*[8] and ACOG distributed to its membership *Preconception and Prenatal Carrier Screening for Cystic Fibrosis: Clinical and Laboratory Guidelines* (see Resources).

The joint ACOG/ACMG guidelines recommend that CF testing should be:

- offered to people with a family history of CF and to reproductive partners of persons with CF,

- offered to couples where one or both partners are Caucasian and are planning a pregnancy or seeking prenatal care, and

- available with appropriate information about limitations to couples in other racial or ethnic groups who are at lower risk and for whom testing is less effective (e.g., Hispanics, African Americans, Asian Americans).

These and more recent[9] guidelines are intended to assist health care providers and laboratories in implementing clinical recommendations. They describe laboratory standards, ways to convey expectations and limitations of testing, and prenatal diagnosis options for identified carrier couples.

Key Facts About CF Carrier Testing

- CF occurs in about 1 in 2,500 Caucasian newborns of European descent.
- Laboratory errors in *CFTR* testing occur at a rate similar to other clinical laboratory tests (U.S. estimate is about 1-2% of test results). Performance may improve with experience and the use of confirmatory testing.[10]
- About 88% of *CFTR* mutations in non-Hispanic Caucasians can be identified by testing for 25 common mutations. In this high-risk group, about 78% of carrier couples can potentially be identified.[11]
- The 25-mutation testing panel identifies a smaller proportion of *CFTR* mutations in other U.S. populations:

Population	Identified using 25 mutation testing panel (%)	
	Carriers	Carrier couples*
Hispanic Caucasian	52	27
African American	42	18
Asian American	24	6

*Estimates assume that both members of the couple are from the same racial/ethnic group, and that both members carry a *CFTR* mutation.

Evaluation of Prenatal CF Screening

To support the transition of molecular technology from research to use in clinical and public health practice, CDC funded a model process to evaluate genetic tests by assembling, analyzing, and reporting available data on safety and effectiveness. The report, *Population-Based Prenatal Screening for Cystic Fibrosis via Carrier Testing*, summarizes what we currently know about using the *CFTR* test for prenatal/preconception carrier testing, and was written for health care professionals, payers, and policy makers (http://www.cdc.gov/genomics/activities/FBR/CF/CFIntro.htm).

2003: Learning from Implementation and Practice

In 2003, a large U.S. genetic testing laboratory and the ACMG focused scientific and media attention on potential problems related to CF carrier testing.[12] For example, it was reported that as many as 20 couples may have had prenatal diagnostic testing (i.e., amniocentesis) that was "unnecessary" based on current guidelines—that is, the couples' risk of having a child with CF was not high enough to warrant a recommendation that those couples consider prenatal diagnosis.[13-16]

There was widespread debate about whether such a problem is more likely to result from (a) misinterpretation of complex testing results by providers, (b) variability in laboratory compliance with existing clinical guidelines, (c) poor communication between laboratories and providers, or (d) clarity and content of reports of DNA test results.[14-16] It should be noted, however, that the extent of this, and other anecdotally-reported implementation issues, remains unclear. Among the tens of thousands of women screened, it is not known what problems are being encountered, nor how frequently. Very little reliable data are currently available on the numbers and characteristics of women using this testing, and even less on outcomes of testing.

Public Health Importance of Lessons Learned

In response to these concerns, the CDC and Mt. Sinai School of Medicine hosted a conference on *Communication: Key to Appropriate Genetic Test Referral, Result Reporting and Interpretation* that focused on CF carrier testing as a model, and the Genetics and Public Policy Center at Johns Hopkins University convened a panel discussion on the use and regulation of CF testing.[17] These events provided an opportunity for interaction between clinicians, laboratory professionals, policy makers, payers, the public health community, and consumers. Some topics included:

Challenges in educating health care providers and consumers:

- Informed health care providers, consumers, payers, policy makers, and others are crucial for ensuring that integration of genetic tests into routine care yields the greatest benefit and results in minimal harm.

- Validated educational materials about genetic tests for health care providers and consumers need to be readily available and usable, in order to ensure that both the provider and the patient understand the benefits and limitations of testing.

- In order to ensure appropriate use of new tests and facilitate smooth integration into routine practice, best practice guidelines must be widely disseminated to laboratories and health care providers, including

specialists and general practice physicians, mid-level practitioners (e.g., midwives, physician assistants, nurse practitioners), nurses and health educators.

Communication between health care providers and laboratories:

- Testing involves many steps: selecting the appropriate genetic test, the process of information and consent, obtaining and forwarding the correct specimen and patient information to a qualified laboratory, performing and reporting the test, and communicating results both to the provider and to the patient.

- Laboratories report difficulty in obtaining key patient information (e.g., reason for testing, family history, race/ethnicity) that is needed to select the appropriate test, and to interpret results correctly.

- Health care providers report variability among laboratories in test ordering and reporting practices and in how patient information is collected and used. They describe a need for test requisitions and reports that are simple and clear, and that use standardized terminology.

Compatibility of clinical and laboratory guidance with U.S. healthcare delivery models:

- Physician offices and clinics may lack resources to support some aspects of CF testing, such as educating patients, documenting consent, and providing access to key resources and expertise (e.g., genetic counseling, diagnostic testing) when appropriate.

- Key patient information must be collected and transmitted to the laboratory; this process may become complicated when, for example, patients leave the doctor's office to have blood drawn.

- Preconception/prenatal CF carrier testing has provided insight into other potential complications related to our health care delivery system. For example, offering testing is recommended for partners of women who have been identified as CF carriers. The partner's sample may be sent to a different laboratory, however, because a different physician has ordered the test or because the partner has different insurance coverage. This raises questions about appropriate linkage and interpretation of the couple's test results, as well as the potential difficulty of monitoring the effectiveness of CF carrier testing in practice—questions that can only be answered by testing surveillance and data collection.

Post-implementation data collection to assess the public health impact of testing:
The number of CF carrier tests performed is increasing rapidly, but good data on utilization, quality, acceptability, and access are lacking. Problems encountered in the transition from research to clinical practice need to be documented and quantified, and the data used to reevaluate the screening process and make timely changes in recommendations and guidelines as needed.

- Population-based data on prevalence of genetic variants in affected and healthy populations are needed to select mutations to be included in genetic testing panels, and to re-evaluate such panels as new data become available. The 25-mutation CF panel is currently under review.

- Test request and reporting formats should facilitate communication between clinicians and laboratories and support proper interpretation of genetic tests.

- U.S. healthcare delivery models that link the patient to medical professionals, laboratory testing, counseling services, and payment options should be examined to assure appropriate services are accessible and cost effective.

- When a genetic test makes the transition from research to practice, appropriate data collection must continue to monitor its quality, acceptability, accessibility, utilization, usefulness, and fit with healthcare delivery models.

In recognition of the significance of the issues raised, additional CDC initiatives are being developed, including efforts to support effective pre-implementation evaluation of tests, facilitate partnerships between laboratories and health care providers, and ensure appropriate ordering, reporting, and use of genetic tests.

Resources

2001 Guidelines and Educational Brochures

Preconception and Prenatal Carrier Screening for Cystic Fibrosis: Clinical and Laboratory Guidelines - October, 2001 ($15, $9 ACOG members)
ACOG Bookstore Professional Resources: http://sales.acog.com/acb/stores/1/

Cystic Fibrosis Carrier Testing: The Decision is Yours
(http://www.acog.org/from_home/wellness/cf001.htm)

Cystic Fibrosis Testing: What Happens If Both My Partner and I Are Carriers?
(http://www.acog.org/from_home/wellness/cf002.htm)

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